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Estrogen screening in evaluation of fetal outcome and infant's development

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1 Introduction

While fetal monitoring by means of sonography and cardiotocography has now been fully established and accepted, varying opinions still exist regarding the use of endocrine methods. The determination of different placental hormones in an effort to reduce fetal mortality has been suggested for many years [4, 9, 12, 17, 18, 25, 26]. Even though the necessity of determining estrogens in serum and/or urine is evident, it is hardly practiced. Based on the results of a prospective study on pregnancy control, it is intended to evaluate several different endocrine methods with focus on the determination of estrogens. In future papers, various placental proteins will be dealt with.

Estriol (E_3) amounting to 85% of estrogens produced during pregnancy is quantitatively the most important of the estrogens. Up to 90% of E_3 is formed on the basis of fetal precursors. From this it would appear that conclusions concerning any fetal condition could most readily be drawn from the determination and interpretation of E_3 concentrations in maternal serum. With regard to this it should be mentioned that the reaction of free serum E_3 is far more sensitive than that of total serum E_3 [11, 13, 22].

Ninety percent of the estrogens to be found in excreted maternal urine are composed of glucuronized estriol, which means that the determination of total estrogen excretion in 24 hours also appears to be the most likely parameter to be assessed. In a high risk group of patients a close connection between E_3 or the urinary estrogens (UE) and fetal emergency situations has been demonstrated [9, 12, 24]. It has not been clarified whether or not it is necessary to carry out screening examinations in all pregnancies. Furthermore, so far no study

Curriculum vitae

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has been carried out to prove whether a connection between the estrogen concentration and early infants' development can be established.

Three issues arise from the following investigation. The first concerns the value of E_3 and UE analysis before the 34th week of gestation for the screening of clinical abnormalities of the fetus at birth. The second concerns the value of serial estrogen measurements after the 34th week of pregnancy and in the last 5 weeks before delivery to detect fetuses at risk. The third concerns the value of estriol measurements to allow a long term prognostication of early infant's development.

2 Materials and methods

During the years 1976 to 1979 all of the women who visited the Outpatient Department at the University Women's Hospital for the first time (before the 20th week of pregnancy) were included in a prospective balanced study. Within this study they were examined regularly, and at the same time blood samples were taken and sonographic examinations carried out. During the last trimester, cardiotocograms were taken and the total urinary estrogen output within 24 hours was determined. Clinical management was in no way influenced by hormone results, which were determined after delivery. Fetal wellbeing was demonstrated by ultrasound, nonstress and contraction stress tests.

In order to obtain relevant data for all the weeks of pregnancy, the study was balanced. Each patient drew a number that made her eligible to enter one of the four sub-groups of the study. Within these groups, certain pregnancy weeks were chosen in which examinations at the clinic were planned and in which blood samples were taken. There were absentees in all groups. A total of 1140 women was included in the study. On account of miscarriages, insufficient examinations and missed appointments, 260 patients were eliminated from the study. Multiple births (n = 11) were not studied, so that the following results of the study are based on 869 patients.

Twelve to 24 months after birth, questionnaires concerning the development of the children were sent to the individual parents. Complete information regarding cause of and response to treatment was requested in cases in which children had required medical attention or had been hospitalized. The results of regular pediatric examinations (8 days, 1, 6, 12, and 24 months) were also integrated in the study. A total of 17 children died immediately following delivery or during the first year of their lives; from a total of 759 children (89%) results were available after one year of observation. At the end of the second year the results from 661 children (78%) were available. The group of the children for whom our data were available after 1 and 2 years was fully comparable to the group of children who did not show up for medical follow-up. Due to the increased perinatal mortality of these children, only the Apgar score was significantly lower in the latter group.

All data relating to pregnancy and delivery as well as the neonate and the infants' development during the first two years of life were computerized at the Heidelberg University Computer Center. E_3 was determined from deep frozen serum. Free E_3 was extracted with diethyl ether and measured by radioimmunoassay with an antiserum against 6-oxoestriol-carbomethoxine-BSA (intraassay precision was below 6%, interassay precision was 7%, sensitivity was 30 pg/ml, cross reactions with various steroids were below 2%). UE was measured with a modified method according to Osawa and Slaunwhite [21] (intra- and interassay precision was 5%). The overall incidence of inadequate urine collection was 5%.

Due to the fact that a relatively large number of analyses was available (2846 E_3 samples taken during the 28th to 40th week of pregnancy), all values were examined up to the time of delivery with regard given to the state of health of the individual fetus. Corresponding examinations were carried out for UE (1940 samples were taken during weeks 28 to 40 of pregnancy). In order to obtain a realistic comparison, only those samples were taken into consideration that had been employed for both methods

within a period of 3 days. Estrogen drops due to antibiotic, dexamethasone or betamimetic therapy were eliminated before calculation. When in a given week of pregnancy more than one result was available, one value was randomly chosen. Evaluation of the estrogen results was in accordance with the following principles:

1. Estrogen concentrations for each individual week of pregnancy were measured.
2. During 28th to 34th week of pregnancy one sample of every patient was chosen at random to evaluate the screening efficiency.
3. Serial determinations made in the 35th to 40th week of pregnancy. The prevalent concentration values were taken into calculation for each patient.
4. Serial determinations during the last 5 weeks prior to delivery were interpreted as shown under 3).

Correlations were made with Spearman Correlation Coefficient (SC), Wilcoxon (WT), Kruskal-Wallis (KW), and chi square tests (ST). Differences with $p < 0.05$ were considered significant.

Sensitivity

$$\frac{\text{Truly positive (TP)} \times 100}{\text{Truly positive (TP) and false negative (FN)}}$$

specificity

$$\frac{\text{Truly negative (TN)} \times 100}{\text{Truly negative (TN)} \times \text{false positive (FP)}}$$

and relative risk

$$\frac{TP}{TP + FP} : \frac{FN}{FN + TN}$$

were calculated for various important variables (Apgar score, growth retardation, intensive care, "at risk").

Estrogen concentration increases during the course of pregnancy. It is not possible to compare the absolute concentration of the individual week of pregnancy, which is why the estrogen level of each week of pregnancy was divided into percentiles. The normal range was determined by 229 women whose singleton pregnancies and deliveries were recorded as uncomplicated (as indicated by the following parameters: delivery at ≥ 37 weeks of pregnancy of an infant $>$ 10th percentile of weight for age and sex, no fetal distress in labour requiring intervention or admission to special care, Apgar scores > 8 at 1 minute and > 9 at 5 and 10 minutes, cord artery pH > 7.20. Pregnancy occured after spontaneous ovulation, no bleeding during pregnancy, no illness recorded during pregnancy, no kind of prescription or other drugs taken during the pregnancy, sonographical examinations showed a gestational age of the individual fetus which corresponded to the estimated age of pregnancy). Low values were defined as below the 10th percentile, normal ones between the 10th and the 90th percentile, high ones above the 90th percentile. In figure 1 median, 10th and 90th percentiles calculated on the basis of this method are shown for E_3 and UE.

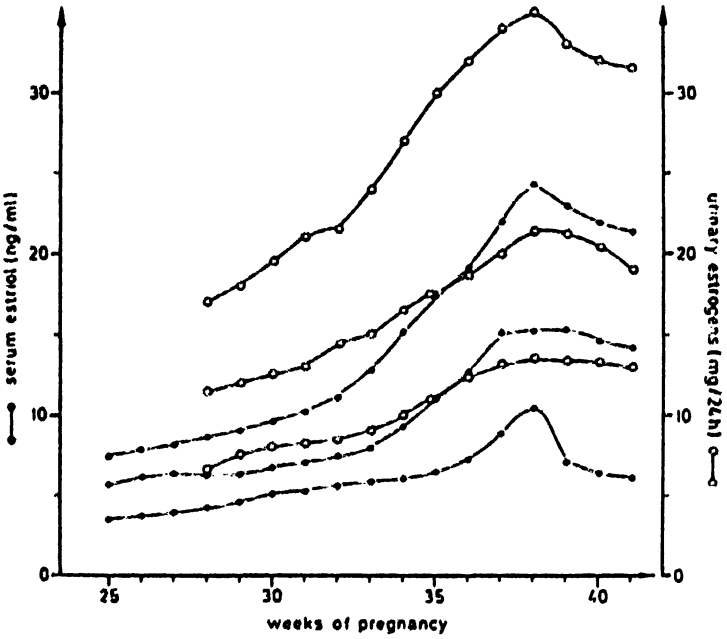

Figure 1. Normal range of E_3 and UE concentrations during weeks 25 and 41 of pregnancy. Median, 10th and 90th percentiles are given.

3 Results

The main clinical data relating to pregnancy and delivery are given in table I. More than 200 variables were checked. Important data

Table I. Clinical data of 869 pregnancies with estrogen screening.

	%		Mean ± SD
Nulliparous	49	Maternal age	27 ± 5 yr
Previous abortions	29	Maternal body weight	60 ± 10 kg
Uncomplicated pregnancies	29	Week of delivery	38.5 ± 2.6
Premature labour	29	Placental weight	600 ± 115 g
Toxemia of pregnancy	26	pH cord artery	7.27 ± 0.07
Delivery ≤ 36th week of pregnancy	10	pH cord vein	7.34 ± 0.07
Postterm pregnancy	2	Birth weight	3250 ± 580 g
Delivery by		Birth height	51 ± 3.7 cm
– Cesarean section (primary)	15 (6)	Heard circumference	35 ± 1.5 cm
– vaginally spontaneous	78	Sex ratio ♂: ♀	51 : 49
– forceps or vacuum	7		
SGA	9		
1′ Apgar score ≤ 7	12		
Postnatal intensive care	14		
Malformations	2		
PM (WHO)	1,5		

Table II. Clinical data of 759 infants one year and of 661 infants two years after birth.

Variables	mean ± SD/%
One year	
Sitting	7 ± 1.4 mth
Standing	9 ± 1.7 mth
Walking	12.8 ± 1.7 mth
Talking > 5 words at age one	61
Neurological sequelae	8
Diseases in the first year	25
Malformations (heart, hip, etc.)	9
Impaired hip joint abduction	16
Cerebral palsy	30
Convulsions	3
Gastro-intestinal and/or pulmonary disorders	42
Two years	
Body weight	12.7 ± 1.6 kg
Body height	90 ± 5 cm
Number of teeth	17.6 ± 2.5
Obvious mental retardation	5
Diseases in the second year	60
Hospitalization in the first 2 years	15
Susceptibility for infections	30
Sleep disorders	12
Convulsions	2
Neurological sequelae with two years	3
Seeing and hearing defects	1.6
Speech disorders	5
Unsatisfactory control of bowel and bladder	33

concerning the children's development in the first and second year are shown in table II. "Cerebral palsy" included asymmetric muscle tone, hypotonia or hypertonia with and without functional disorders. At the age of two years "neurological sequelae" were only diagnosed in cases with functional disorders. Children with major malformations or Down's syndrome have not been considered in the description of the 2 years' development.

Statistical analyses of these data revealed that the infants' development up to two years of age was significantly influenced by prematurity, toxemia, cesarean section, low placental weight, low birth weight, low pH of the cord blood, and low Apgar scores. Therefore, the correlation of all the factors mentioned above with maternal estrogen levels was studied in detail.

3.1 Estriol (E_3)

3.1.1 Weekly determination

For each of the weeks 28 to 40 of pregnancy a close connection between E_3, the weight of the placenta (SC 0.3, $p < 0.01$) and the infants' weight at birth (SC 0.25, $p < 0.005$) was demonstrated. Only during weeks 28, 30, 32 and 35 to 39 there was a significant correlation to the

Apgar values (WT $p < 0.001$). There was no correlation found with regard to prematurity, toxemia or pH of the umbilical vein and artery.

3.1.2 E_3 screening (weeks 28–34 of pregnancy)

The significant results are compiled in table III, in which, above all, the infants' weight and the Apgar score are recorded. There was no correlation between the infants' sex, the duration of pregnancy, method of delivery or umbilical vein and artery pH.

Reduced E_3 concentrations were measured in 11% of the cases, normal ones in 80%, and increased ones in 9%. The frequency of reduced E_3 concentrations was more than double in newly born small for gestational age (SGA) compared to adequate for gestational age (AGA) infants (table IV).

Mothers of children with a poor Apgar score 1 minute post partum suffered twice as much from reduced E_3 concentrations (table V). In cases in which the Apgar score was still low after 10 minutes the rate was 3 times higher.

Because of premature births, growth retardation, low Apgar score and neonatal complications, 29% of all children in the study had to be considered to be at risk. The mothers had almost twice as frequently reduced E_3 concentrations as compared with normal pregnancies. One third of the newborns with pulmonary complications were delivered by mothers with low estriol values. In order to correctly evaluate the significance of an E_3 screening, the sensitivity, specificity, and relative risk are given in table VI. The specificity was high for all parameters

Table III. Significant correlations between E_3 levels (screening during weeks 28–34 of pregnancy) in 869 pregnancies and variables at delivery. SC = Spearman Correlation Coefficient. KW = Kruskal-Wallis test.

Variable	Level of significance	
	P	
Placental weight	0.0001	(SC 0.30)
Birth weight	0.0001	(SC 0.28)
Birth height	0.0001	(SC 0.20)
Head circumference	0.05	(SC 0.18)
Apgar 1′ after birth	0.005	KW
Apgar 5′ after birth	0.005	KW
Apgar 10′ after birth	0.0001	KW
Postnatal intensive care	0.005	KW

Table IV. Estriol screening and birth weight of the newborn (n = 869). Division of weight percentiles according to THOMSON [27] into: SGA (< 10th percentile), AGA (10th–90th percentile) and LGA (> 90th percentile).)(² = 17.337.
$p < 0.005$

Estriol value	birth weight %		
	SGA	AGA	LGA
	9	84	7
Low	18	80	2
Normal	7	86	7
High	4	84	12

Table V. Estriol screening and Apgar scores in 869 pregnancies.

Estriol value	Apgar score after delivery %			
	1 min		10 min	
	≤ 7	≥ 8	≤ 9	10
Low	23	77	18	82
Normal	11	89	4	96
High	12	88	6	94
)(²	10.470		24.935	
P	0.001		0.0001	

Table VI. Diagnostic relevance of estriol screening in 869 pregnancies.

Variable	%		
	Sensitivity	Specificity	Relative risk
1′ Apgar score	21	91	2.18
5′ Apgar score	22	90	2.33
10′ Apgar score	34	91	4.27
SGA	23	91	2.57
Intensive care	20	91	2.09
"At risk"	17	92	3.10

tested. The sensitivity was low, ranging from 17% in detecting infants at risk to 34% in babies with reduced Apgar scores 10 minutes after birth.

None of the variables characterizing the infants' development 1 and 2 years after birth revealed significant correlations with the E_3 screening. However, within the group of newborns with poor Apgar scores 1 and 10 minutes post partum, it was noticed that the children of mothers who had reduced E_3 concentrations had a higher illness rate during the first year of their lives, and their power of speech was deficient at the end of the first year compared to those of mothers with normal E_3 values. Furthermore, every other child had already been in a hospital by 2 years, and after normal values it was only every 9th. With regard to bowel and bladder control the children with poor Apgar scores and reduced E_3 concentrations lagged behind those children whose mothers had normal E_3 concentrations.

3.1.3 E_3 serial determinations (weeks 35—41 of pregnancy)

In addition to the E_3 screening, serial determinations during weeks 35 to 40 were performed in 423 pregnant women. As can be taken from table VII, the sensitivity of this method to detect infants at risk increased, whereas the specificity decreased and the relative risk remained almost unchanged compared to the E_3 screenings. If only those children are taken into consideration that needed postnatal intensive care,

Table VII. Serial E_3 determinations (weeks 35—41 of pregnancy) for detecting infants at risk in 423 pregnancies.

Variable	%		
	Sensitivity	Specificity	Relative risk
1′ Apgar score	26	85	1.76
5′ Apgar score	29	85	2.10
10′ Apgar score	40	85	3.42
SGA	31	85	2.28
Intensive care	30	86	2.17

Table VIII. Development of the infants up to 2 years in relation to serial estriol assays (weeks 35 to 41 of pregnancy), P = percentile for normal pregnancies.

Variables of development	no of infants	% serum estriol			level of significance	% urinary estrogens			level of significance
		< 10. P	10.—90. P	< 90. P		< 10. P	10.—90. P.	> 90. P	
Ill during first year of life	185	40	23	15	0.01	–	–	–	n. s.
Retarded speech development	288	49	34	20	0.01	44	38	17	0.05
Ill during second year of life	398	71	56	42	0.05	–	–	–	n. s.
Hospitalization during first two years of life	102	30	15	11	n. s.	–	–	–	n. s.
Physiotherapy up to two years of age	18	18	5	0	0.05	14	2	0	0.01
Poor bowel and bladder control at age 2	215	50	35	20	0.02	–	–	+	n. s.
Underweight at age 2	55	21	8	6	0.005	26	11	6	0.05

respiratory distress occurred in a total of 31% after reduced E_3 serial assays and in only 6% after normal E_3 levels.

In the first year, children following reduced E_3 serial assays showed a significantly higher incidence of illness (40%) than those following normal (23%) or increased (15%) E_3 (WT, $p < 0.01$). The percentage of retarded speech power was higher after low E_3 values than after normal or increased E_3 values (table VIII). At two years of age, no difference in speech development could be found. There was no difference with respect to sleep patterns. At the end of the second year, more children had been ill after reduced E_3 concentrations than after normal values, infections of the lung and digestive system being the most frequent diagnoses. Hospitalization during the first two years of life appeared to be more frequent after low E_3 values; the difference was, however, not significant. Though the motor development was independent of estriol concentrations, neurological sequelae with functional handicaps up to two years of life was most frequent after low E_3 levels. The development of bowel and bladder control following reduced E_3 serial assays was slower as compared to pregnancies with normal and increased E_3. There was a significant correlation between the infants' weight at two years of age and E_3 concentrations. The parameters of physical growth did not differ.

3.1.4 E_3 serial determinations (last 5 weeks before delivery)

As the infants' development was strongly influenced by prematurity and Apgar scores, the role of E_3 was tested with a view to these parameters. All premature children with reduced Apgar scores and low E_3 concentrations were ill at one stage during the first year of their lives, retarded in speech at the age of one, and low of weight at the age of two, while the premature children with low Apgar scores and normal E_3 values developed normally. 90% of the premature children with good Apgar scores had normal E_3 concentrations and an uncomplicated development up to two years of age. The disease rate of mature children of mothers with low E_3 concentrations was twice as high during the first year of life (above all pulmonary disorders and intestinal infections) compared to those of mothers with normal E_3 concentrations. The risk of being speech-retarded was even three times higher. However, no differences were discovered between the babies of these groups in respect to muscle tone, movement, reflexes or cranial nerves.

Taking into account the decreasing period of time between the E_3 determination and delivery, the significance of the method increased. So up to 50% of the SGA could be found and up to 60% of the reduced Apgar scores, provided the determination was performed in the last 2 weeks before delivery.

3.2 Urinary estrogens (UE)

3.2.1 Weekly determination

Only after the 34th week of gestation was there a significant connection with the weight percentile for age and sex (KW $p < 0.001$). The remaining variables of pregnancy and delivery showed no significance.

3.2.2 UE-screening (weeks 28–34 of pregnancy)

Only a remote connection (ST, $p < 0.05$) could be shown between UE on one hand and Apgar score or percentile of birth weight on the other

Table IX. Diagnostic relevance of urinary estrogen determinations during weeks 28–34 of pregnancy in 654 pregnancies.

Variable	%		
	Sensitivity	Specificity	Relative risk
1′ Apgar score	17	92	2.00
5′ Apgar score	16	91	2.48
10′ Apgar score	18	91	2.07
SGA	19	92	2.50
Intensive care	15	92	2.30
"At risk"	17	94	2.02

hand. With regard to this, it was demonstrated that lower Apgar values and a smaller weight percentile occurred more frequently after reduced UE than after normal or even increased values. Table IX shows the sensitivity, specificity, and relative risk of the most important variables of delivery. The significance was not as high as it was in the case of the E_3 determination. No significant correlation with the development of the child in the first two years was found.

3.2.3 UE serial determinations (weeks 35–41 of pregnancy)

No significant correlation with the Apgar scores, the weight percentiles or the remaining variables could be demonstrated. In table X the important results of this part of the study are given. With regard to the development of the individual children a correlation of reduced UE to retarded speech, physiotherapy at the age of two and low body weight at the age of two could be demonstrated (table VIII).

The correlation coefficient (SC) between E_3 and UE varied in the weeks 30 to 40 of pregnancy from 0.3 to 0.47 ($p < 0.0005$). With regard to all examined parameters the importance of the E_3 determination was greater than that of UE.

Table X. Serial UE determinations (weeks 35–41 of pregnancy) for detecting infants at risk in 397 pregnancies.

Variable	% Sensitivity	Specificity	Relative risk
1′ Apgar score	9	93	1.36
5′ Apgar score	11	94	1.66
10′ Apgar score	6	91	1.58
SGA	14	94	2.03
Intensive care	13	93	1.70

4 Comment

In the following, only a limited comparison of our data with the results of other authors is possible. The definition of so-called normal range varies greatly. It has to be taken into account that there is a logarithmic distribution for hormone concentrations and not a standard distribution, so that averages and single or double standard deviations would not be accurate. For this reason, percentiles for the classification of hormone levels were chosen. Although, according to this definition, in the normal group of patients 10% of the hormone values were decreased, the group of patients being at risk was expected to be large enough for statistical analysis.

In other studies, the normal group of patients is usually not defined as strictly as defined here, with the complete data variations to the individual course of pregnancy and birth being taken into account. Usually, the majority of studies do not deal with an unselected population, but with small groups of patients at risk, as for instance gestosis or diabetes. Finally, studies of various other authors cannot be used for comparison, as these authors determined total estrogens in serum which does not render such definite results [8, 9, 11, 17]. In keeping with numerous other studies [5, 10, 16, 19] our investigations also showed evidence of retarded development during the first two years of the infant's life in cases of premature birth, intrauterine growth retardation, low Apgar score or cesarian section. Due to this, it was here attempted to find the appropriate method of determining estriol to allow a correct prognostic evalution of the condition of the infant at birth and in its early two years development.

For the estriol screening of the study, the 28th to 34th week of pregnancy were chosen as at this time there is an increased risk for the unborn due to intrauterine asphyxia or premature birth. At the same time the chances of extrauterine survival are still limited. During this period, there was already a significant correlation between E_3 concentration and the babies' birth weight observed, which could not be demonstrated by UE analysis. It needs to be mentioned that the mothers of only 23% of all SGA children had reduced E_3 concentrations. It was possible to improve the sensitivity of the method through serial determinations of E_3,

the level of which could be used to mark the relationship to growth. 50% of the IUGR fetuses could be diagnosed by E_3 one to two weeks before birth. When interpreting these results, it must be pointed out that the specificity is less satisfactory in serial determinations, i. e. an increasing number of below normal results can be found in infants with normal weight.

HARDY et al [15] came to the same conclusion as reached here with regard to E_3 analysis beyond the 37th week of pregnancy. They obtained an even better correlation when the childrens' sex, the size of the mother, and the parity were taken into consideration.

After the 34th week of pregnancy there was also evidence of a significant correlation of UE with birthweight, although this could not be demonstrated in serial determinations and was also far more inaccurate than was the case with E_3. BEISCHER [4] described the results of UE analysis among 6361 woman in the 32nd and the 36th weeks of pregnancy. He observed that lower birth weight was more frequent when the maternal estriol levels were low (21.7%) than compared to cases with normal estriol levels (6.6%).

A significant connection to babies' Apgar scores at birth could be shown for the E_3 screening tests. Lower E_3 concentrations were significantly correlated to a low Apgar score 10 minutes after birth. This is understandable since only grave disorders of the newly born cannot be compensated in the first 10 minutes post partum. Depending on the individual period of time elapsed until birth, 60% of the babies with low 10 minute Apgar scores could be traced back to mothers having low E_3 concentrations.

BASHORE and WESTLAKE [2] monitored 321 risk pregnancies through regular analysis of E_3 from the 32nd week of pregnancy until birth. They found that the prognostic value was highest when obtaining blood samples during the last week before birth. If E_3 was below 4 ng, which is probably comparable with our 5th percentile, there was a significant correlation to the occurrence of neonatal problems in all groups who were at risk, except for the group with diabetes. They calculated a 50–80% sensitivity for this method. By determination of total E_3 in plasma, EDWARDS et al [9] could prove a connection with Apgar levels, too. This was also true after correction of the influence of individual birth weight [12].

The UE excretion of the patients proved to have only minor relation to Apgar scores. Even with serial determination the UE were often normal when E_3 was already below normal. As the scores varied so greatly, it must be assumed that this was due to inadequate urine collection, although the most obvious mistakes to be made during collection were eliminated. By means of UE excretion method BEISCHER and BROWN [3] recognized one third of all babies with bad Apgar scores in 140 cases of risk pregnancies. AICKIN et al [1] compared the plasma estrogen analysis with UE excretion and found that the correlation with fetal emergencies was almost identical with both methods. Even though the latter authors could prove a highly significant correlation between the two levels in 454 recorded analyses, they found relevant discrepancies between serum and urine estrogens in many cases. In some studies a better clinical analysis was achieved when serum estrogens in combination with urine estrogens were used to predict fetal emergencies. The estrogen/creatinine ratio in early morning samples of urine could possibly improve the UE method [20, 23].

According to the E_3 screening and serial determinations, the children of mothers with a low E_3 level had an increased incidence of neonatal complications. Thirty two percent of the 19 children with respiratory distress syndrome had mothers with low hormone levels. The predictive value of UE was less satisfactory. The remaining perinatal risk factors for the children's development (premature birth, acidosis, cesarean section) could not be diagnosed through either of the methods mentioned.

With respect to the infant's development in the first two years, it was only possible in isolated cases to show significant correlations to hormone levels determined from blood samples before the 34th week of pregnancy. Considering the group of children with poor Apgar scores

one minute or 10 minutes after birth, it was striking that with low E_3 screening levels the children proved to have a higher incidence of illness in their first year, they were more often in a hospital and were retarded in speech and bowel and bladder control. Serial E_3 determinations in late pregnancy as well as during the last 5 weeks before birth revealed significant correlations between low E_3 levels and illness in the first 2 years of life, retarded speech power, neurological sequelae up to 2 years because of functional handicaps, and low body weight at age two. Training of bowel and bladder control appeared to be less efficient in this group. Even after correction of socio-economic factors these differences remained unchanged. The correlation to UE was less significant. With both E_3 methods no differences were observed with regard to the sleep patterns, motoric development, seeing and hearing abilities.

To our knowledge the development of children in relation to the maternal E_3 concentration has not yet been examined. In some previous studies with 14 or 34 patients, some connection between low UE and psychomotoric development disorders have been reported [14, 29, 30]. TROLLE et al [28] published follow-up studies on 110 children (8 to 14 years old) with previously determined level of maternal UE during pregnancy. In 27.3% of the cases severe handicaps were observed after low UE levels had been registered compared to 1.8% after normal UE levels. Speech disorders were found in 12.7% after low UE values compared to 1.8% and disorders of seeing or hearing in 20% compared to 3.6%. Low et al [19] observed a reduced mental and physical development at 12 months of age in babies of lowest birth weights with extremely low maternal urinary estrogen.

From this study it becomes evident that prognostic statements about the well-being of the fetus at birth can be obtained more accurately through E_3 analysis than through UE analysis. While cases of premature birth cannot be discovered with these methods, intrauterine growth retardation and fetal emergencies can be detected to a certain degree. As the evidence of growth retardation is easier to obtain with ultrasound, the main importance of E_3 analyses lies in the prognosis of possible Apgar scores at birth and early infant's development. As the actual state of the fetus is easily and inexpensively obtained by nonstress/contraction stress test, E_3 values will usually not influence clinical management [6]. Even in diabetic patients where estriol drops are supposed to precede fetal jeopardy [13] the clinical usefulness of E_3 determinations was doubtful [7]. Due to the low sensitivity of the E_3 method and in view of cost-benefit-calculations an E_3-screening of every pregnant woman cannot be recommended. In pregnancies at risk, however, serial E_3 determinations once weekly in addition to ultrasound and nonstress testing allow a better prognostication of fetal well-being. In the case of reduced E_3 values maximum postpartum care should be made available for all infants with poor Apgar scoring. The early infants' development should be given special attention. Follow-up studies of the children of age four are under way and will include observations of physical growth, intellectual development and neurological assessment in addition to evaluation of vision, hearing and speech.

Summary

In an unselected obstetric population of 869 women serial determinations of estriol in serum and urine were performed from the 28th week of pregnancy until delivery. Clinical management was based on ultrasound and nonstress/contraction stress tests only. Data on the development of the infants were available after 1 year in 759 cases (89%) and after 2 years in 661 cases (78%). Serum free estriol (E_3) screening during weeks 28–34 of pregnancy revealed a significantly increased risk for reduced Apgar scores, growth retardation and postnatal complications in pregnancies with decreased levels ($p < 0.001$). The development of the children was disturbed by a higher incidence of childhood diseases, retardation in speech and bowel and bladder control. The urinary estrogen determinations (UE) during this period of pregnancy showed only a vague connection with birth weight and Apgar scores ($p < 0.05$) and no connection to the infant's development. Serial determinations of E_3

after the 35th week of pregnancy increased the significance for all parameters tested. If the estrogen concentration was determined in the last 2 weeks before delivery, 50% of the SGA and 60% of the endangered cases could be diagnosed. After reduced E_3 serial levels neurological sequelae, reduced body weight, retarded speech and late development of bowel and bladder control were significantly more frequent at age two than after normal E_3 levels. The differences obtained by serial UE determinations were less evident. Considering cost-benefit-calculations, an E_3 screening of every pregnant woman cannot recommended. In pregnancies at risk serial E_3 determinations allow better prognostication of fetal well-being. In the case of reduced E_3 values maximum post partum care should be made available for all newborns. Special support should be given to the early infant's development after reduced E_3 values have been observed.

Keywords: Follow-up, maternal estrogen concentrations, perinatal period.

Zusammenfassung

Östrogenbestimmung in der Schwangerschaft: Aussagefähigkeit in Bezug auf den kindlichen Zustand bei der Geburt und die Entwicklung in den ersten zwei Lebensjahren

Bei einer Gruppe von 869 nicht selektierten schwangeren Frauen wurden routinemäßig die Serumöstriolkonzentration (E_3) und die Gesamtöstrogenausscheidung im 24 Std.-Harn (UE) von der 28. Schwangerschaftswoche bis zur Entbindung bestimmt. Die Ergebnisse lagen erst nach der Geburt vor, so daß sich das klinische Management auf den Ultraschall und das CTG (in Ruhe und ev. nach Oxytocin-Belastung) stützte. Daten über die kindliche Entwicklung standen nach 1 Jahr in 759 Fällen (89%) und nach 2 Jahren in 661 Fällen (78%) zur Verfügung. Wurden zwischen 28.—34. Schwangerschaftswoche erniedrigte E_3-Konzentrationen gefunden, so war das Risiko erniedrigter Apgarwerte, von Wachstumsretardierung und von postnatalen Komplikationen signifikant erhöht ($p < 0{,}001$). Die kindliche Entwicklung wurde beeinträchtigt durch eine höhere Inzidenz von Kinderkrankheiten, Verzögerung der Sprachentwicklung und der Sauberkeitserziehung. Während desselben Zeitraums wiesen die UE lediglich einen vagen Zusammenhang mit dem Geburtsgewicht und den Apgar-Werten ($p < 0.05$) auf und keinen Zusammenhang mit der kindlichen Entwicklung. Bei Bestimmungen von E_3 nach der 35. Schwangerschaftswoche erhöhte sich die Signifikanz bei allen untersuchten Parametern. In den letzten zwei Wochen vor der Entbindung wiesen 50% der Mütter mit SGA und 60% der Mütter mit durch Asphyxie gefährdeten Feten erniedrigte E_3 auf. Nach wiederholt niedrigen E_3-Konzentrationen waren im Alter von 2 Jahren neurologische Probleme, niedriges Körpergewicht und eine verzögerte Sprach- und Sauberkeitsentwicklung signifikant häufiger als nach normalen E_3-Werten. Die serienmäßige UE-Bestimmung brachte weniger deutliche Unterschiede. Im Hinblick auf die Kosten-Nutzen-Relation kann eine E_3-Überwachung bei jeder Schwangeren nicht empfohlen werden, bei Risikoschwangerschaften ist damit jedoch eine bessere Prognostizierung des kindlichen Befindens möglich. Bei niedrigen E_3-Werten sollte für alle Neugeborenen eine optimale postnatale Versorgung verfügbar sein. Die frühkindliche Entwicklung sollte nach niedrigen E_3-Werten besonders gefördert werden.

Schlüsselwörter: Mütterliche Östrogenkonzentrationen, Nachuntersuchung, Neonatalperiode.

Résumé

Surveillance œstrogènique dans l'évaluation du devenir fœtal et du développement infantile

Dans un groupe de 869 femmes enceintes non sélectionnées le taux d'œstriol sérique (E_3) ainsi que l'élimination des œstrogènes totaux dans les urines de 24 heures (UE) ont été dosés de façon systématique de la 28ème semaine de gestation jusqu'à l'accouchement.

Les résultats n'étaient disponibles qu'après l'accouchement, alors que la surveillance clinique était effectuée par l'ultrasonographie et la cardiotocographie (au repos et eventuellement après une charge en oxytocine). Les données sur le développement infantile étaient disponibles après un an dans 759 des cas (89%) et après deux ans dans 661 des cas (78%).

Si entre la 28ème et la 34ème semaine de gestation les concentrations d'E_3 se trouvaient diminuées, le risque d'un score d'Apgar diminué, d'un retard de croissance et de complications postnatales étaient augmentés de façon significative ($P < 0{,}001$).

Le développement infantile a été entravé par une incidence accrue de maladies infantiles, d'un retard de développement du langage ainsi que d'un retard dans l'éducation de la propreté. Pendant ce même temps les UE présentaient seulement une relation vaque avec le poids de naissance et le score d'Apgar ($P < 0{,}05$) et aucune relation avec le développement infantile. Lors des dosages d'E_3 après la 35ème semaine de gestation la signification de tous les paramètres mesurés fut augmentée. Pendant les deux dernières semaines avant l'accouchement 50% des mères avec SGA et 60% des mères avec fœtus en menace d'asphyxie montraient un E_3 diminué. Après des dosages répétés de concentrations d'E_3 diminuées,

des troubles neurologiques, un retard pondéral et un développement du langage et d'éducation de la propreté retardés, étaient significativement plus fréquents à l'âge de deux ans qu'après des valeurs d'E_3 normaux. Le dosage en série d'UE rapportait moins de différences évidentes. Au point de vue d'une relation coût-bénéfice, une surveillance d'E_3 ne peut pas être recommendée chez chaque femme enceinte, toutefois, en cas de grossesse à risque, cette méthode permet un meilleur pronostic à long terme du bien être infantile.
En cas d'E_3 abaissé, des soins postnataux optimaux devraient être disponible pour tout nouveau-né. Après des valeurs basses d'E_3 le développement de la première enfance devrait être particulièrement encouragé.

Mots-clés: Concentration maternelle d'œstrogènes, examen médical postnatal, période néonatale.

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